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LYCOPODIUM ALKALOIDS—V

THE STRUCTURE AND STEREOCHEMISTRY OF FAWCETTIINE, CLAVOLONINE AND RELATED ALKALOIDS

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Abstract Fawcettiine, clavolonine and annofoline have been interrelated and their stereochemistries elucidated. The conversion of clavolonine to lycopodane, the Wolff–Kishner reduction product of lycopodine is described and a structure is proposed for an abnormal Hofmann degradation product of clavolonine.

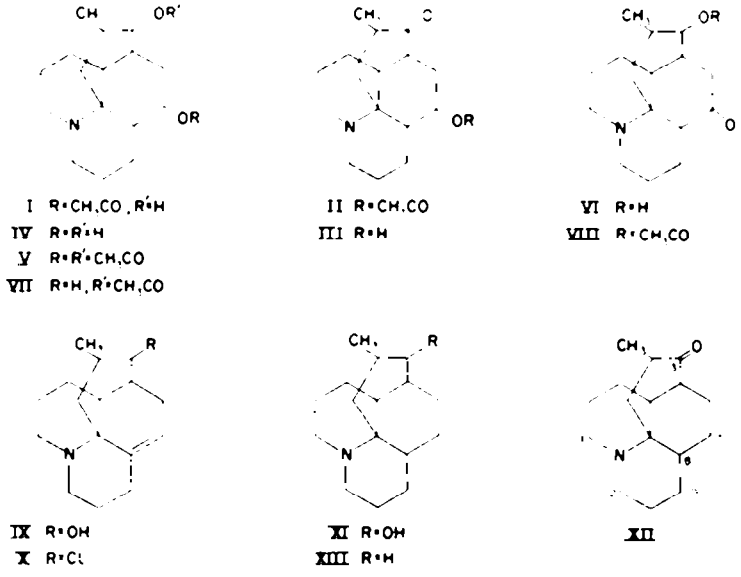
FAWCETTIINE, $C_{18}H_{29}NO_3$ the major alkaloid of *L. fawcettii*[1] and a minor component of *L. annotinum*[2,3] and Jamaican *L. clavatum*[4] has been shown to be a tetracyclic tertiary base possessing a hydroxyl group and an O-acetyl residue. Mild hydrolysis of the alkaloid affords deacetylfawcettiine, $C_{16}H_{27}NO_2$ which is also naturally occurring in Jamaican *L. clavatum*.[3] Acetylation of deacetylfawcettiine or fawcettiine gives rise to the diacetate Base K, $C_{20}H_{31}NO_4$ found naturally in L. fawcettii.[3]

From the chromium trioxide oxidation of fawcettiine, a ketoacetate dehydrofawcettiine, $C_{18}H_{27}NO_3$ was isolated which hydrolysed readily in base to a compound $C_{16}H_{25}NO_2$. The infra-red spectrum of the latter in Nujol bore a strong resemblance to that of annofoline[2] but was clearly not identical and the melting points were also different. However, the infra-red spectrum in chloroform solution was identical to that of annofoline in this solvent and the optical rotation ($[\alpha]_D$ 132°) was in good agreement with the published value for annofoline ($[\alpha]_D$ 131°).[2] Subsequently, it was found that crystallization from a concentrated ethereal solution gave material showing an infra-red spectrum in Nujol identical to that published for annofoline.* When the methiodide of the hydrolysis product was compared with that of annofoline the two were shown to be identical (melting and mixed melting points and infra-red curves). More recently[5] Anet and Khan have shown annofoline to have the structure (III) so that dehydrofawcettiine must be (II) and fawcettiine (I). Deacetylfawcettiine and Base K must be (IV) and (V) respectively. In an effort to corroborate the identity of annofoline and deacetyldehydrofawcettiine, annofoline acetate was prepared but its methiodide (m.p. 289–290° $[\alpha]_D$ 66°) was found to be different from dehydrofawcettiine methiodide (m.p. 271–272° $[\alpha]_D$ −48°). Since annofoline can be reduced to deacetylfawcettiine,[5] the difference between annofoline acetate and dehydrofawcettiine must be stereochemical rather than skeletal (see later).

* The melting point (and the infra-red spectrum in Nujol) of annofoline are somewhat variable. Dr. Anet (Private communication) has also observed this phenomenon, which is presumably dependent on the equilibrium between the hemi-ketal and hydroxy-ketone forms of this base (see ref. 5).

[1] R. H. Burnell, *J. Chem. Soc.* 3091 (1959).
[2] F. A. L. Anet and N. H. Khan, *Canad. J. Chem.* 37, 1589 (1959).
[3] R. H. Burnell, B. S. Mootoo and D. R. Taylor, *Canad. J. Chem.* 38, 1927 (1960).
[4] R. H. Burnell and B. S. Mootoo, *Canad. J. Chem.* In press (1961).
[5] F. A. L. Anet and N. H. Khan, *Chem. & Ind.* 1238 (1960).

Clavolonine, $C_{16}H_{25}NO_2$ was obtained as a major component of Jamaican *L. clavatum*,[4] and is also a tetracyclic tertiary base which from the infra-red spectrum contains a hydroxyl and a carbonyl in a six-membered (or larger) ring. Oxidation of clavolonine with chromium trioxide–pyridine gave a diketone, $C_{16}H_{23}NO_2$, characterized as the methiodide, m.p. 310–312° which was identical to the methiodide of the diketone obtained (albeit in low yield) by the similar oxidation of deacetylfawcettiine (IV). This ketone could have arisen from a compound epimeric to annofoline or from either epimer corresponding to VI. Of these, the latter seemed the more likely since clavolonine shows a peak at 1410 cm^{-1} in the infra-red, suggestive of a methylene grouping adjacent to the carbonyl. The following conversion of deacetylfawcettiine to clavolonine clearly distinguishes between these possibilities.



Acetylation of deacetylfawcettiine in acetic anhydride–pyridine at room temperature (or using the acetic anhydride–sodium acetate method) affords Base K but if the reaction is carried out at 5° a new monoacetate, isofawcettiine is produced which may be further acetylated to Base K or hydrolysed back to deacetylfawcettiine. Isofawcettiine (which must be VII) was oxidized to the corresponding ketone VIII, dehydroisofawcettiine, hydrolysis of which gave a substance identical in every respect to clavolonine. This shows the latter to be VI and (unlike annofoline) the O-acetyl derivative of clavolonine was shown to be identical to dehydroisofawcettiine. Reduction of clavolonine with an ethereal solution of lithium aluminium hydride afforded (as the only product) deacetylfawcettiine (IV), whereas lithium in liquid ammonia[6] or sodium in isobutanol gave the epimeric α-dihydroclavolonine, m.p. 263–266°.

Deacetylfawcettiine is readily dehydrated by thionyl chloride in benzene to give an unsaturated alcohol, anhydrodeacetylfawcettiine, $C_{16}H_{25}NO$[1]. The NMR trace of the latter shows that the double bond bears only one proton (τ, 4·45) and also that the grouping CH_3—C –H is preserved (τ, 9·00; J 5·9 cps) so that the anhydro product is IX. This is contrary to our findings[3] that fawcettiine can be dehydrated and then

[6] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* 75, 1282 (1953).

hydrolysed to anhydrodeacetylfawcettiine but one must assume that in the work-up from the phosphorus pentoxide dehydration both hydrolysis and acid catalysed elimination must have occurred. Confirmation of structure (IX) for anhydrodeacetylfawcettiine was obtained by the ready elimination of water from isofawcettiine (thionyl chloride in benzene) followed by hydrolysis to IX. The best method for the preparation of IX was found to be treatment of deacetylfawcettiine with ethyl chloroformate to give the mono-ester, followed by thionyl chloride dehydration and then hydrolysis. The anhydro compound obtained from deacetylfawcettiine directly was accompanied by smaller amounts of an unsaturated chlorine containing substance, $C_{16}H_{24}NCl$ for which we tentatively propose the structure (X). Prolonged refluxing of anhydrodeacetylfawcettiine in a benzene solution of thionyl chloride also produced the same chloro compound.

A comparison of the optical rotations of a series of compounds obtainable from lycopodine and a similar series from clavolonine (see Fig. 1) led us to believe clavolonine to be a hydroxy lycopodine and the stereochemistry of the ring systems of the two alkaloids to be the same. The rotations of the corresponding methiodides reflect the same relationship.

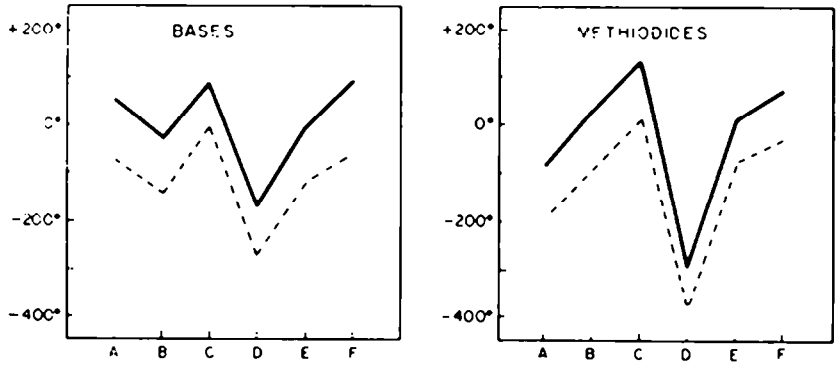


FIG. 1. Molecular rotation comparison of clavolonine (—) and lycopodine (· —) derivatives. A: ketone; B: lithium aluminium hydride reduction product; C: sodium in alcohol reduction product; D: anhydro compound (dehydration of B with thionyl chloride); E: acetate (acetic anhydride–pyridine treatment of B); F: Wolff–Kishner reduction product.

This similarity of the two bases was confirmed as follows: Wolff-Kishner reduction of clavolonine (VI) afforded the dihydrodeoxyclavolonine (XI) which was smoothly oxidized to the corresponding ketone (XII). The latter was again subjected to Wolff–Kishner reduction and the product, a mobile oil characterized as the methiodide, m.p. 284–286°. The infra-red spectrum of this derivative was indistinguishable from that of the corresponding derivative of lycopodane (XIII), obtained from lycopodine and a mixed melting point of the methiodides showed no depression. In our hands, lycopodine when subjected to the same conditions as used for the Wolff–Kishner reduction of clavolonine, yielded only the hydrazone, previously reported by Marion[7a] but Ayer[7b] and co-workers have been able to effect the reduction in one step. However we found lycopodine hydrazone to be converted smoothly to lycopodane by heating

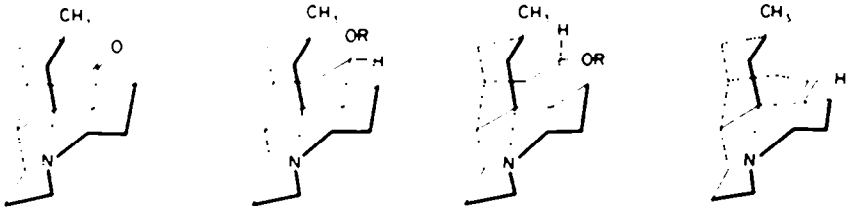
[7a] D. B. MacLean, R. H. F. Manske and L. Marion, *Canad. J. Res.* **28B**, 460 (1950); [b] W. A. Ayer and G. G. Iverach, Personal communication.

in a sealed tube at 190–195° with ethanolic sodium ethoxide. The ketone (XII) can be reduced to dihydrodeoxyclavolonine (XI) in high yield by sodium in diethylene glycol.

Wolff–Kishner reduction of dehydrofawcettiine afforded, as the only product a compound, $C_{16}H_{27}NO$, which is isomeric but not identical to dihydrolycopodine (XVa). Anet[8] has also described this reduction product and has suggested the structure (XXII) (CH_2 for C:O) since it is also obtained by similar reduction of annofoline.

It was hoped to correlate clavolonine and lycopodine by reducing both with red phosphorus in hydriodic acid but the only tractable product from clavolonine analysed for $C_{16}H_{25}NI_2$ and normal methods for the removal of iodine have so far proved ineffective.

From MacLean's work on lycopodine,[9] the stereochemistry of the molecule is readily deduced to be XIV which accounts for the hindered nature of the carbonyl and the internal cyclization of α-cyanobromolycopodine. The dihydrolycopodine (m.p. 168°) (XVa) obtainable by the lithium aluminium hydride reduction of lycopodine undoubtedly has the hydroxyl group axial since elimination proceeds readily in benzene containing thionyl chloride at room temperature to give anhydrodihydrolycopodine (XVII). When sodium in isobutanol is used for the reduction, the epimeric α-dihydrolycopodine (XVIa) is produced which is not readily dehydrated but does form a cathylate with ethyl chloroformate in pyridine.[10] Dihydrolycopodine (XVa) does not react with the latter even after 24 hr. The infra-red spectra of the acetyl derivatives (chloroform solution) are in agreement with this since XVb shows a split acetate whereas XVIb shows only a single peak in the 1250 cm^{-1} region.[11]

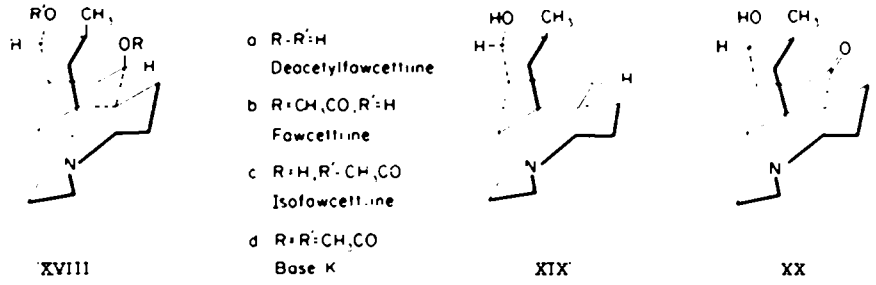


XIV XV a R=H b R=CH_3CO XVI a R=H b R=CH_3CO XVII

Clavolonine is reduced by lithium aluminium hydride in ether to deacetylfawcettiine and by sodium in isobutanol to α-dihydroclavolonine, these reactions are analogous to the respective reductions of lycopodine. Clavolonine affords an acetate (single acetate peak) and forms a cathylate with ethyl chloroformate. Dehydration is not accomplished with thionyl chloride nor even by phosphorus pentoxide in boiling toluene. The facile dehydration of IV to anhydrodeacetylfawcettiine shows the hydroxyl at C_7 to be *axial* and *trans* to the C_8 hydrogen atom. Since IV, which reacts with ethyl chloroformate at one of the hydroxyl groups only, forms the monoacetate (VII) (single acetate peak) which is unaffected by ethyl chloroformate in pyridine then the readily acetylated hydroxyl group is equatorially disposed to the bridge ring. Fawcettiine (I) reacts readily with ethyl chloroformate and shows a complex acetate peak in the infra-red.

[8] F. A. L. Anet, *Tetrahedron Letters* No. 20, 13 (1960).
[9] W. A. Harrison and D. B. MacLean, *Chem. & Ind.* 261 (1960).
[10] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Utne, *J. Amer. Chem. Soc.* **74**, 3309 (1952).
[11] H. Hirschmann, *J. Amer. Chem. Soc.* **74**, 5357 (1952).

Thus, this group of bases is accommodated satisfactorily by XVIIIa-d, anhydrodeacetylfawcettiine by XIX and clavolonine by XX.



XVIII XIX XX

From the infra-red spectrum of clavolonine in chloroform solution and in particular its resemblance to that of annofoline, it was thought[12] that both of these bases existed as equilibria between hydroxy-ketone and hemiketal forms but quantitative infra-red comparison spectra in chloroform (Fig. 2) show that the hemi-ketal form of clavolonine makes a very small contribution, if indeed it is present at all.

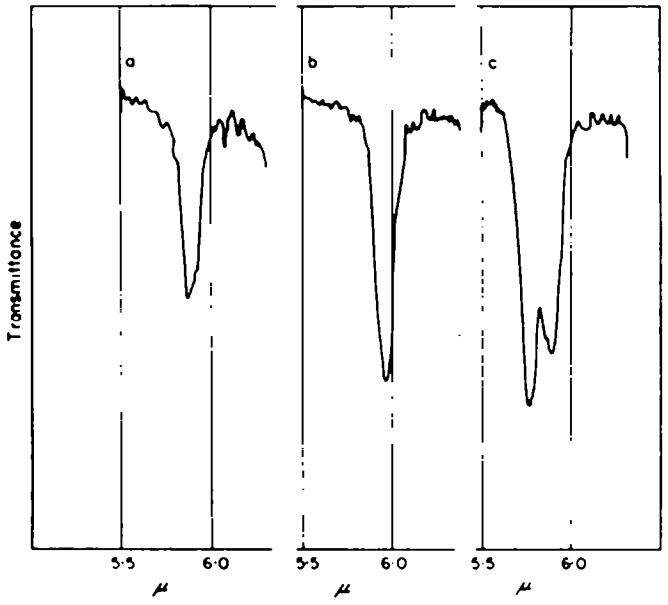


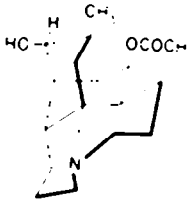
FIG. 2. Comparison of the intensities of the carbonyl absorption in the infra-red spectra of (a) annofoline (b) clavolonine and (c) acetyl clavolonine. The concentration of the base is 20 mg/ml in each case (chloroform solution).

Lofoline,[2] which has been shown to be epimeric to fawcettiine[8] and thus XXI, dehydrates readily as would be expected of a compound containing an *axial* hydroxyl group with an adjacent *trans* hydrogen substituent. Lofoline does not form a cathylate.

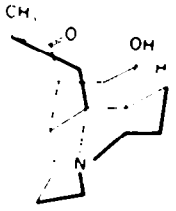
Optical rotatory dispersion measurements on clavolonine and lycopodine show that both exhibit positive Cotton effects. Applying Djerassi's Octant Rule[13] to these

[12] R. H. Burnell and D. R. Taylor, *Chem. & Ind.* 1239 (1960).
[13] C. Djerassi, *Optical Rotatory Dispersion* p. 178. McGraw-Hill, New York (1960).

findings suggests the absolute stereochemistry of these bases to be as shown (XX and XIV) rather than the mirror-image representations which have been used in previous publications.* Negative Cotton effects are shown by dehydrofawcettiine (II) and the ketone (XII) in agreement with the proposed absolute stereochemistry. Annofoline, which necessarily contains the bridge ring in the boat form since this base exists in both the hemi-ketal and hydroxy-ketone forms, also shows a negative Cotton effect and must clearly be XXII. The change of ring conformation (from the chair form in fawcettiine and dehydrofawcettiine) must involve inversion of the configuration of



XXI



XXII

XXIII

the adjacent methyl grouping, since an *axial* (flag-pole) methyl group alpha to the carbonyl would produce a positive Cotton effect. The stereochemical difference between annofoline acetate and dehydrofawcettiine referred to earlier, must arise during the basic hydrolysis of the latter. Under these conditions the hemi-ketal form of annofoline is greatly favoured and this explains why annofoline is the only product from the hydrolysis. The acetylation of annofoline is considerably more complex if carried out in the presence of added bases such as pyridine or sodium acetate but refluxing in acetic anhydride alone affords annofoline acetate in high yield.

Lycopodium alkaloids in general, have shown no great susceptibility to Hofmann degradation. Refluxing clavolonine methiodide in tertiary butanol containing potassium t-butoxide afforded a crystalline product, $C_{17}H_{27}NO_2$ m.p. 196–198° which contained one N-methyl group (analysis), a carbonyl and a hydroxyl (infra-red). The NMR spectrum, showed no bands at low field ascribable to olefinic protons and the infra-red spectrum contained no peaks characteristic of a terminal methylene grouping. Since the product contains an N-methyl grouping, fission of either the C_1 –N or the C_{12} – N bonds must have occurred but the potential propene side-chain must have cyclized intramolecularly. Both clavolonine and the Hofmann base show infra-red peaks at 1410 cm^{-1} which suggests the presence of the grouping $-CH_2C{:}O$. This band does not appear in the infra-red spectrum of the lithium aluminium hydride reduction product obtained from the Hofmann product nor in deacetylfawcettiine (the reduction product from clavolonine). Complete reduction of the carbonyl grouping of the Hofmann base by this method requires considerably longer refluxing than the reduction of clavolonine, suggesting a greater degree of hindrance to the approaching reagent. The optical rotatory dispersion of the Hofmann product shows a negative Cotton effect, as opposed to the positive effect in clavolonine, indicating the introduction of an axially disposed substituent adjacent to the carbonyl group. This evidence is consistent with the structure (XXIII) for the Hofmann base.

* Dr. Z. Valenta has informed us that the University of New Brunswick workers have deduced this same absolute stereochemistry.

EXPERIMENTAL

The infra-red figures were measured as Nujol mulls unless otherwise stated and the pK titrations were performed in 50% aqueous MeOH. Melting points are uncorrected and the optical rotations were measured at 28–30°.

Dehydrofawcettiine (II)

A solution of fawcettiine (2·4 g) in pyridine (30 ml) was added slowly to a slurry of chromium trioxide (4 g) in pyridine (40 ml) while the temperature was maintained below 20°. The mixture was stirred at room temperature for 9 hr and then made basic with ammonia and extracted with chloroform. The crude product obtained by evaporation of the latter (2·24 g) was run over alumina in benzene affording solid dehydrofawcettiine (1·6 g) and on further elution unchanged fawcettiine (0·41 g). The dehydrofawcettiine was recrystallized from acetone, m.p. 139–140°, $[\alpha]_D$ + 68° (*c* 1·12, EtOH), I.R. 1740 and 1240, 1225 (acetate) 1710 (C:O) cm^{-1}. R.D. in EtOH (*c* 0·045) 25°; $[\alpha]_{700}$ 51°, $[\alpha]_{589}$ + 84°, $[\alpha]_{515}$ 1000°, $[\alpha]_{396}$ 194°). Found: C, 71·0; H, 9·4; O, 15·5; N, 4·5. $C_{16}H_{21}NO_3$ requires: C, 70·8; H, 8·9; O, 15·7; N, 4·6%).

The methiodide, m.p. 271 272° (inserted at 250°), $[\alpha]_D$ + 48 (*c* 1·49, 50% EtOH). (Found: C, 51·2; H, 6·8; N, 3·1; I, 28·6. $C_{16}H_{21}NO_3.CH_3I$ requires: C, 51·0; H, 6·8; N, 3·1; I, 28·4%).

Annofoline (by hydrolysis of II)

To dehydrofawcettiine (1·37 g) in MeOH was added a solution of sodium hydroxide (10 g) in MeOH (25 ml) and water (45 ml). After 16 hr at room temperature, the turbid solution was diluted with water and extracted with chloroform. Concentration gave an oil (1·2 g) which solidified on standing. The annofoline, after recrystallization from ether had m.p. 150–151°, $[\alpha]_D$ 132 (*c* 1·05, EtOH), I.R. 3450 (OH) and 1704 (C:O) cm^{-1}. The infra-red spectra in Nujol and in chloroform were identical to those of annofoline. R.D. in EtOH (*c* 0·2) 24°; $[\alpha]_{700}$ 94·5, $[\alpha]_{589}$ −130·5°, $[\alpha]_{305}$ −1135°, $[\alpha]_{396}$ −905°.

The methiodide, from MeOH–acetone, m.p. 308–310° (inserted at 240°). (Found: C, 50·0; H, 7·0; N, 3·6; I, 31·8. $C_{16}H_{23}NO_3.CH_3I$ requires: C, 50·4; H, 7·0; N, 3·5; I, 31·3%).

Annofoline acetate methiodide

Annofoline (100 mg) was refluxed for 5 hr in acetic anhydride. After removing the solvent *in vacuo* the residue was dissolved in benzene and run through a short alumina column. The eluate, which showed only one spot on paper, was converted to the methiodide, m.p. 289–290° (inserted at 250°), $[\alpha]_D$ 66° (*c* 1·31, 50% EtOH). (Found: C, 50·9; H, 6·9; N, 2·9. $C_{16}H_{21}NO_3.CH_3I$ requires: C, 51·0; H, 6·8; N, 3·1%).

Dehydroclavolonine

(a) *From deacetylfawcettiine.* Deacetylfawcettiine (795 mg) was dissolved in pyridine (7·5 ml) and the solution added to pyridine (15 ml) containing chromium trioxide (1·5 g), the temperature being kept at 20°. The mixture was stirred at room temperature for 2 hr, then poured into water, made strongly basic with sodium hydroxide and chloroform extracted. Evaporation gave the crude base (570 mg) which was run over alumina in benzene to give the dione (140 mg) as an oil. Further elution afforded unreacted deacetylfawcettiine (270 mg). The dione readily formed the methiodide, m.p. 310 312° (decomp., inserted at 250°) identical in every respect to that obtained in (b).

(b) *From clavolonine.* Clavolonine (2·27 mg) was oxidised as in (a) yielding largely unchanged starting material (1·5 g) and the dione (0·41 g). The methiodide, m.p. 310·312° (decomp., inserted at 250°), showed absorption in the I.R. at 1725 and 1707 (C:O) cm^{-1}. (Found: C, 50·2; H, 6·6; N, 3·6; O, 8·2; I, 31·6; N·Me, 3·8. $C_{16}H_{23}NO_3.CH_3I$ requires: C, 50·6; H, 6·5; N, 3·5; O, 7·9; I, 31·5; N-Me, 3·7%).

Acetylation of deacetylfawcettiine

(a) *At room temperature.* Deacetylfawcettiine (377 mg) was dissolved in pyridine and acetic anhydride added. After 16 hr at room temperature the solution was evaporated to dryness and the oil (410 mg) run over alumina in benzene. The first eluate (60 mg) was shown by its melting point, 113–117°, mixed melting point and infra-red spectrum to be Base K, V. Further benzene elution gave a white crystalline solid (240 mg) which was a mixture of Base K and isofawcettiine (VII) (102 mg),

separated by fractional sublimation. The latter was sublimed for analysis, m.p. 207–208°, $[\alpha]_D$ −48° (*c* 0·87, EtOH). I.R. 3100 (OH) and 1724, 1235 (acetate) cm^{-1}. I.R. in carbon tetrachloride 3100, 1726 and 1240 (sharp single band) cm^{-1}. (Found C, 70·5; H, 9·5; O, 15·6; O–Ac, 14·3. $C_{18}H_{30}NO_3$ requires: C, 70·3; H, 9·5; O, 15·6; O Ac, 14·9%).

The methiodide, m.p. 288–289° was prepared in acetone. (Found C, 50·7; H, 7·5; I, 28·5. $C_{19}H_{33}NO_3.CH_3I$ requires: C, 50·8; H, 7·2; I, 28·2%.)

(b) *At low temperature.* Deacetylfawcettiine (1·23 g) was acetylated as above but the temperature was kept at 5° for 20 hr. The crude oil obtained showed only one spot on paper chromatography and after running over alumina, gave an almost quantitative yield of isofawcettiine (1·35 g).

Hydrolysis of VII (20 mg) in MeOH (1 ml) and water (1 ml) containing sodium hydroxide (0·5 g) gave deacetylfawcettiine, m.p. 205–207° (mixed m.p. and infra-red).

Dehydroisofawcettiine (VIII)

Isofawcettiine (0·67 g) was oxidized with chromium trioxide (1·5 g) in pyridine as described above. The crude product (0·5 g) was purified by alumina chromatography affording a colourless oil (0·4 g), I.R. in chloroform, 1724 and 1245 (sharp single peak -acetate), 1698 (C:O) cm^{-1}, characterized by conversion to the methiodide, m.p. 308° (inserted at 250°). (Found: C, 50·6; H, 7·0; N, 3·2; O, 11·4; I, 28·2. $C_{19}H_{27}NO_3.CH_3I$ requires: C, 51·0; H, 6·8; N, 3·1; O, 11·7; I, 28·4%).

Hydrolysis of VIII *to clavolonine* (VI)

Dehydroisofawcettiine (200 mg) was dissolved in MeOH (10 ml) and a solution of sodium hydroxide (5 g) in water (10 ml) was added. After 4 hr the mixture was diluted with water and chloroform extracted to yield a white solid (160 mg) which after sublimation had m.p. 234–235° (unchanged on admixture with clavolonine). R.D. in EtOH (*c* 0·05) 25°; $[\alpha]_{440}$ · 40, $[\alpha]_{310}$ + 2440°, $[\alpha]_{300}$ · 1310°. The infra-red traces in nujol and chloroform were identical to those of clavolonine.

Clavolonine acetate methiodide Clavolonine (100 mg) was acetylated in acetic anhydride–pyridine at room temperature for 18 hr. The crude acetate (140 mg) was purified by alumina chromatography affording an oil (125 mg) showing an identical infra-red spectrum to dehydroisofawcettiine (chloroform solution). The methiodide, m.p. 308° (decomp.) was not depressed on admixture with dehydroisofawcettiine methiodide of the same melting point.

Reduction of clavolonine

(a) *With lithium aluminium hydride.* To clavolonine (195 mg) in anhydrous ether was added excess lithium aluminium hydride and the mixture refluxed for 16 hr. Wet MeOH was used to decompose the unreacted hydride and after filtration, the solution was taken to dryness and triturated with acetone. Evaporation of the filtered acetone solution gave white crystals, m.p. 206–207°, $[\alpha]_D$ −6° (*c* 1·0 EtOH) after sublimation (180 mg). Paper chromatography, infra-red comparison and mixed m.p. showed this material to be deacetylfawcettiine.

The methiodide (not previously described), m.p. 289–290° (decomp.), $[\alpha]_D$ −1·5° (*c* 1·37 50% EtOH). (Found: C, 50·1; H, 7·6; I, 31·3. $C_{16}H_{27}NO_3.CH_3I$ requires: C, 50·1; H, 7·4; I, 31·2%).

Sodium borohydride in methanol gave the same product but the reaction was complete only after refluxing for 3 hr.

(b) *With sodium in isobutanol.* Clavolonine (500 mg) was dissolved in dry toluene (60 ml) and anhydrous isobutanol (0·75 ml) added. This solution was added to a suspension of sodium (100 mg) in toluene (3 ml) and the mixture stirred overnight. Water was added and the toluene layer taken to dryness to give an oil (200 mg) which was run over alumina in benzene. Some unchanged clavolonine (15 mg) was first eluted in chloroform and subsequent elution with MeOH afforded α-dihydroclavolonine (70 mg), m.p. 263–266°, $[\alpha]_D$ + 33° (*c* 1·01 EtOH), I.R. 3370 and 3100 (*sh*) cm^{-1}. A sample was sublimed for analysis. (Found: C, 72·7; H, 10·4; O, 12·6. $C_{16}H_{29}NO_3$ requires: C, 72·4; H, 10·3; O, 12·1%).

Reduction of clavolonine by lithium in liquid ammonia gave the same α-dihydroclavolonine but in low yield.

Anhydrodeacetylfawcettiine (IX)

(a) *From isofawcettiine.* Isofawcettiine (100 mg) was dissolved in benzene and excess thionyl chloride added. After 4 hr the solution was evaporated to dryness and the residue taken up in water, basified with ammonia and chloroform extracted. The brown oil (100 mg) was purified by alumina

chromatography, giving anhydroisofawcettiine (80 mg) as a colourless oil. A portion of the material was converted to the methiodide, m.p. 258–261°, identical with acetylanhydrodeacetylfawcettiine methiodide (see later).

The bulk of the material (50 mg) was hydrolysed at room temperature in methanolic sodium hydroxide affording IX (40 mg).

(b) *From deacetylfawcettiine.* IV (700 mg) was dissolved in pyridine and excess ethyl chloroformate added. After 6 hr at room temperature the solution was taken to dryness *in vacuo* and the residue suspended in water, basified with ammonia and extracted with chloroform. The crude ester was run over alumina in benzene and a small part sublimed for analysis, m.p. 195–196°, I.R. 3100 (*sh.* OH), 1737 and 1258 (ester) cm^{-1}. (Found: C, 67·4; H, 9·3; O, 19·1; O-Et, 13·5. $C_{16}H_{21}NO_4$ requires: C, 67·6; H, 9·3; O, 19·0; O-Et, 13·4%).

The remaining ester was treated with excess thionyl chloride in benzene at room temperature for 4 hr and the unsaturated ester obtained by evaporation and extraction. After hydrolysis in methanolic sodium hydroxide at room temperature the crude product was run over alumina in benzene giving first an unidentified oil (80 mg) and then the anhydrodeacetylfawcettiine IX (550 mg) as a white solid, m.p. somewhat variable but ca. 75–85°, $[\alpha]_D$ −70° (*c* 1·18 EtOH). (Found: C, 77·6; H, 10·1; N, 5·4; O, 6·8; pK, 9·7. $C_{16}H_{23}NO$ requires: C, 77·7; H, 10·2; N, 5·7; O, 6·5%).

The methiodide, m.p. 263–265° (from MeOH). (Found: C, 52·5; H, 7·5; N, 3·9; I, 32·6. $C_{16}H_{23}NO.CH_3I$ requires: C, 52·5; H, 7·3; N, 3·6; I, 32·6%).

Acetylation of anhydrodeacetylfawcettiine

Treatment of IX (50 mg) with pyridine (4 ml) and acetic anhydride at room temperature for 20 hr gave an oil showing acetate peaks at 1730 and 1250 cm^{-1} in the infra-red (chloroform solution) which was run over alumina and converted to the methiodide, m.p. 258–261°. (Found: C, 52·7; H, 7·1; O, 7·6; I, 29·2; O Ac, 10·3. $C_{18}H_{27}NO_2.CH_3I$ requires: C, 52·9; H, 7·0; O, 7·4; I, 29·4; O Ac, 10·0%).

Chlorodeoxyanhydrodeacetylfawcettiine (X)

After room temperature treatment of IV (704 mg) with thionyl chloride in benzene for 6 hr and evaporation of the volatile constituents, the residue was taken up in water, basified with ammonia and extracted with chloroform. The crude base (680 mg) was chromatographed in benzene over alumina affording first an intractable oil (30 mg) and then a solid (70 mg) showing no hydroxyl band in the infra-red. A sublimed sample had m.p. 126–128°, $[\alpha]_D$ −130° (*c* 1·04 EtOH). (Found: C, 72·4; H, 9·4; O, 0·0; Cl, 13·5. $C_{16}H_{24}NCl$ requires: C, 72·3; H, 9·1; O, 0·0; Cl, 13·3%).

Further elution of the column gave IX (500 mg). Room temperature treatment of IX with thionyl chloride in benzene for 12 hr produced only very small amounts of the chloro compound (X) but treating IX (130 mg) with the same reagents under reflux for 16 hr gave, after chromatography mainly X (87 mg).

Anhydrolofoline

Lofoline dehydrated readily in thionyl chloride and the product, obtained as described previously, converted to the methiodide, m.p. 261–264° (decomp.). I.R. 1728, 1253 and 1238 (acetate) cm^{-1}. (Found: C, 53·1; H, 7·0; N, 2·9. $C_{19}H_{27}NO_2.CH_3I$ requires: C, 52·9; H, 7·0; N, 3·2%).

Wolff Kishner reduction of clavolonine

Sodium (0·4 g) in diethylene glycol was heated to 180° and anhydrous hydrazine distilled into the solution until it refluxed freely at 180°. Clavolonine (0·9 g) was added to the cooled solution which was then refluxed for 16 hr. Excess hydrazine was distilled from the reaction flask until the liquid temperature reached 215–220° and refluxing continued for 24 hr. The cooled solution was diluted with water and chloroform extracted. The chloroform was washed with water, dried over sodium sulphate and evaporated to give the solid dihydrodeoxyclavolonine (XI) (0·66 g) which was recrystallized from acetone, m.p. 164–167° and then sublimed for analysis, $[\alpha]_D$ +14° (*c* 1·73 EtOH). I.R. 3380 and 3070 (OH and bonded OH) cm^{-1}. (Found: C, 77·0; H, 10·8; N, 5·9; O, 6·7. $C_{16}H_{27}NO$ requires: C, 77·1; H, 10·9; N, 5·6; O, 6·7%).

Lycopodane (XIII)

(a) *From dihydrodeoxyclavolonine.* The base (XI) (0·66 g) in pyridine (10 ml) was added to a cold slurry of chromium trioxide (3·3 g) in pyridine (15 ml) and the oxidation continued with occasional

shaking for 6 hr at room temperature. The product (0·4 g) was obtained in the usual manner and purified over a short alumina column. The ketone (XII) (350 mg) showed I.R. absorption at 1707 (C:O) cm^{-1}. R.D. of a sublimed sample, in EtOH (*c* 0·057) 25°; $[\alpha]_{589}$ −211°, $[\alpha]_{317}$ −1320°, $[\alpha]_{310}$ −1250°.

The ketone (270 mg) was subjected to the Wolff-Kishner reduction as described above, affording (after alumina chromatography) a colourless oil (XIII) (150 mg), $[\alpha]_D$ 31·5° (*c* 0·92 EtOH), showing neither carbonyl nor hydroxyl peaks in the infra-red. For characterization, the methiodide was prepared, m.p. 287°, $[\alpha]_D$ −20° (*c* 0·86 EtOH). (Found: C, 54·6; H, 8·2; N, 3·7; I, 34·0. Calc. for $C_{16}H_{27}N.CH_3I$: C, 54·4; H, 8·1; N, 3·7; I, 33·8%).

Mixed melting points with lycopodane methiodide obtained from lycopodine hydrazone, and a sample of lycopodane methiodide from Dr. W. A. Ayer gave no depression and the infra-red spectra were identical.

During the Wolff-Kishner reduction, a colourless oil (30 mg) distilled from the reaction flask with the excess hydrazine. Paper chromatography showed this to be lycopodane and it formed the same methiodide as described above.

(b) *From lycopodine.* Wolff-Kishner reduction of lycopodine (250 mg), employing the conditions described for clavolonine, gave a crude product (235 mg) showing a strong band at 1635 (C:N) cm^{-1} in the infra-red (chloroform solution) which was presumably lycopodine hydrazone. The latter (110 mg) was dissolved in excess ethanolic sodium ethoxide and heated in a sealed tube at 190–195° for 12 hr. After dilution and extraction, the oily product was sublimed and the volatile sublimate (XIII) (100° at 0·2 mm) converted to the methiodide, m.p. 286–287°, which showed no depression in melting point when mixed with the methiodide from (a).

Wolff–Kishner reduction of dehydrofawcettiine

Dehydrofawcettiine (370 mg) was reduced as described above and the crude dihydrodeoxyannofoline (280 mg) recrystallised from acetone, m.p. 194–195°, $[\alpha]_D$ −34·5° (*c* 0·87 EtOH), I.R. 3220 (OH) cm^{-1}. (Found: C, 77·4; H, 10·3; O, 6·9; pK 9·9. $C_{16}H_{27}NO$ requires: C, 77·1; H, 10·9; O, 6·4%).

Reduction of clavolonine (red phosphorus and hydriodic acid)

Clavolonine (170 mg) was refluxed in AR hydriodic acid containing red phosphorus (0·6 g) for 100 hr. After cooling and filtering, the solution was basified with ammonia and chloroform extracted. The oil obtained on evaporation, crystallized on contact with acetone and was recrystallized from this solvent for analysis. The crystalline product, although homogeneous as shown by paper chromatography, had no definite melting point but decomposed over a wide range above 170°. (Found: C, 39·8; H, 5·1; N, 3·0; I, 52·4. $C_{16}H_{28}NI_3$ requires: C, 39·6; H, 5·2; N, 2·9; I, 52·3%).

Formation of cathylates

The procedure used for the reaction of deacetylfawcettiine with ethyl chloroformate was followed. The products were examined by paper chromatography and in the infra-red (chloroform solutions).

Hofmann degradation of clavolonine

To a solution of potassium (2·3 g) in dry tertiary butanol was added clavolonine methiodide (2·0 g) and the mixture refluxed for 60 hr and then evaporated to dryness under reduced pressure. The residue was taken up in water and extracted with chloroform, which was dried and then evaporated. The residue was recrystallized from acetone (550 mg). A portion was sublimed for analysis, m.p. 170–171°, $[\alpha]_D$ −30° (*c* 1·28 EtOH), I.R. 3500 (OH), 1685 (C:O) and 1425 (CH_3–CO) cm^{-1}. No absorption in the U.V. R.D. in EtOH (*c* 0·036) 25°; $[\alpha]_{589}$ −84°, $[\alpha]_{328}$ 1340°, $[\alpha]_{313}$ −980°. (Found: C, 73·6; H, 9·7; N, 5·0; O, 11·8; N-Me, 4·8. $C_{17}H_{27}NO_2$ requires: C, 73·6; H, 9·8; N, 5·0; O, 11·5; N-Me, 5·4%).

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